

Amendments to the Claims:

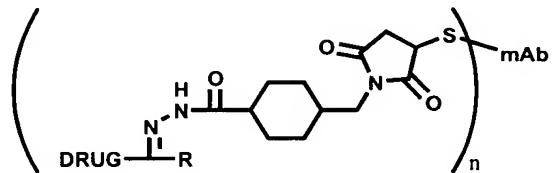
This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Original) A conjugate of an anthracycline drug and an antibody, wherein said anthracycline drug and said antibody are linked via a linker comprising a hydrazide and a maleimide.

2. (Original) The conjugate of claim 1, wherein said linker is 4-(N-maleimidomethyl)cyclohexane-1-carboxyl hydrazide.

3. (Original) The conjugate of claim 1 having the formula:



4. (Original) The conjugate of claim 1, wherein the mAb is directed against a tumor-associated antigen.

5. (Original) The conjugate of claim 4, wherein said tumor-associated antigen is targeted by an internalizing antibody.

6. (Original) The conjugate of claim 1, wherein said conjugate targets carcinomas, sarcomas, lymphomas, leukemias, gliomas or skin cancers

7. (Original) The conjugate of claim 6, wherein said skin cancer is a melanoma.

8. (Currently amended) The conjugate of claim 4, wherein said tumor-associated antigen is selected from the group consisting of CD74, CD22, EPGEGP -1, CEA, colon-specific antigen-p mucin (CSAp), carbonic anhydrase IX, HER-2/neu, , CD19, CD20, CD21, CD23, CD25, CD30, CD33, CD40, CD45, CD66, NCA90, NCA95, CD80, alpha-fetoprotein

(AFP), VEGF, EGF receptor, PIGF, MUC1, MUC2, MUC3, MUC4, PSMA, GD2, GD3 gangliosides, HCG, EGP-2, CD37, HLA-D-DR, CD30, Ia, Ii, A3, A33, Ep-CAM, KS-1, Le(y), S100, PSA, tenascin, folate receptor, Tn and Thomas-Friedenreich antigens, tumor necrosis antigens, tumor angiogenesis antigens, Ga 733, IL-2, , MAGE, and a combination thereof.

9. (Currently amended) The conjugate of claim 8, wherein said tumor-associated antigen is selected from the group consisting of CD74, CD19, CD20, CD22, CD33, ~~EPGE~~~~GP~~-1, MUC1, CEA and AFP.

10. (Original) The conjugate of claim 4, wherein said tumor-associated antigens comprise lineage antigens (CDs) of B-cells, T-cells, myeloid cells, or antigens associated with hematologic malignancies.

11. (Original) The conjugate of claim 1, wherein the antibody is selected from the group of LL1, LL2, L243, C2B8, A20, MN-3, M195, MN-14, anti-AFP, Mu-9, PAM-4, RS7, RS11 and 17-1A..

12. (Original) The conjugate of claim 1, wherein said linker is attached to a reduced disulfide bond on the antibody.

13. (Original) The conjugate of claim 1, wherein said anthracycline drug is selected from the group consisting of daunorubicin, doxorubicin, epirubicin, 2-pyrrolinodoxorubicin, morpholino-doxorubicin, and cyanomorpholino-doxorubicin.

14. (Original) The conjugate of claim 13, wherein said anthracycline drug is linked to the antibody through the 13-keto moiety.

15. (Original) The conjugate of claim 12, wherein said reduced disulfide bond is an interchain disulfide bond on the antibody.

16. (Original) The conjugate of claim 1, wherein the antibody is murine, chimeric, primatized, humanized, or human.

17. (Original) The conjugate of claim 16, wherein the antibody is a fragment of an IgG.

18. (Original) The conjugate of claim 16, wherein the antibody is directed against B-cells.

19. (Original) The conjugate of claim 18, wherein the antibody is directed against an antigen selected from the group consisting of CD19, CD20, CD21, CD22, CD23, CD30, CD37, CD40, CD52, CD74, CD80, and HLA-DR.

20. (Original) The conjugate of claim 19, wherein the antibody is LL1, LL2, L243, C2B8, or hA20.

21. (Original) The conjugate of claim 1, wherein there are 6 - 10 molecules of anthracycline drug per molecule of antibody.

22. (Original) The conjugate of claim 1, wherein the antibody-anthracycline conjugate is internalized into target cells.

23. (Original) The conjugate of claim 22, wherein the antibody-anthracycline conjugate is internalized into target cells, and the antigen is then re-expressed on the cell surface.

24. (Original) The conjugate of claim 1, wherein the overall electric charge of the antibody is not changed.

25. (Original) The conjugate of claim 1, wherein the anthracycline drug bears an alkylating moiety.

26. (Original) The conjugate of claim 25, wherein the alkylating moiety is an enamine.

27. (Original) The conjugate of claim 26, wherein the anthracycline drug is 2-pyrrolino-doxorubicin.

28. (Original) A process for producing the conjugate of claim 1, wherein the linker is first conjugated to the anthracycline drug, thereby producing an anthracycline drug-linker conjugate, and wherein said anthracycline drug-linker conjugate is subsequently conjugated to a thiol-reduced monoclonal antibody or antibody fragment.

29. (Original) The process of claim 28, wherein the anthracycline drug-linker conjugate is not purified prior to conjugation to the thiol-reduced monoclonal antibody or antibody fragment.

30. (Original) A process for preparing the conjugate of claim 1, wherein secondary reactive functional groups on the anthracycline drug are not compromised.

31. (Original) A process for preparing the conjugate of claim 1, wherein alkylating groups on the anthracycline drugs are not compromised.

32. (Original) A process for preparing the conjugate of claim 1, wherein said antrhacycline drug is 2-pyrrolino-doxorubicin, morpholino-doxorubicin or cyanomorpholino-doxorubicin.

33. (Original) A method for treating disease in a mammal comprising administering a conjugate of an antibody and an anthracycline drug of claim 1.

34. (Original) The method of claim 33, wherein said mammal is a human.

35. (Original) The method of claim 33, wherein the antibody-drug conjugate is administered intravenously, intra-peritoneally, intra-arterially, intra-theccally, intra-vesically, or intra-tumorally.

36. (Original) The method of claim 33, wherein the antibody-drug conjugate is given as a bolus or as an infusion.

37. (Original) The method of claim 33, wherein the antibody-drug conjugate is given on a repeat and/or cyclical basis.

38. (Original) The method of claim 33, wherein the mammal is suffering from a cancer.

39. (Original) The method of claim 33, wherein the mammal is suffering from skin cancer, head-and-neck cancer, lung cancer, breast cancer, prostate cancer, ovarian cancer, endometrial cancer, cervical cancer, stomach cancer, colon cancer, rectal cancer, bladder cancer, brain cancer, pancreatic cancer, lymphatic system cancer, sarcoma or melanoma.

40. (Original) The method of claim 33, wherein the mammal is suffering from a B- or T-cell cancer.

41. (Original) The method of claim 40, wherein the mammal is suffering from non-Hodgkin's lymphoma, Hodgkin's disease, lymphatic leukemia, myeloid leukemia or multiple myeloma.

42. (Original) The method of claim 39, wherein the mammal is suffering from melanoma.

43. (Original) The method of any one of claims 33 to 42, wherein the antibody-anthracycline conjugate is administered preceded by, concomitantly with, or subsequent to other standard therapies.

44. (Original) The method of claim 43, wherein said standard therapy is selected from the group consisting of radiotherapy, surgery and chemotherapy.

45. (Original) A method for treating disease in a mammal comprising administering two or more conjugates of an antibody and an anthracycline drug that target different antigens or different epitopes of the same antigen on the same diseased cells.

46. (Original) A method for treating disease in a mammal comprising administering a conjugate of an antibody and an anthracycline drug preceded by, concomitantly with, or subsequent to a second antibody-based treatment, such that the second antibody in the second antibody-based treatment targets a different antigen or a different epitope on the same antigen on diseased cells than the antibody in the conjugate.

47. (Original) The conjugate of claim 1, wherein said antibody is a monoclonal antibody.

48. (Original) The conjugate of claim 1, wherein said antibody is an antibody fragment.

49. (Original) The conjugate of claim 1, wherein said antibody is an antibody fusion protein.

50. (Original) The conjugate of claim 49, wherein said antibody fusion protein is multivalent.

51. (Original) The conjugate of claim 49, wherein said antibody fusion protein is multispecific.

52. (Original) The conjugate of claim 49, wherein said antibody fusion protein comprises two or more of the same or different natural or synthetic antibody, single-chain antibody or antibody fragment segments with the same or different specificities, wherein said antibody or antibody fragment is selected from the group consisting of LL1, LL2, M195, MN-3, RS7, 17-1A, RS11, PAM-4, KC4, BrE3, MN-14, Mu-9, Immu 31, CC49,, Tn antibody, J591, Le(y) antibody and G250.

53. (Original) A kit comprising a conjugate of a monoclonal antibody and an anthracycline drug in a suitable container, wherein said anthracycline drug and said antibody are linked via a linker comprising a hydrazide and a maleimide.

54. (Original) The kit of claim 53, wherein the monoclonal antibody-anthracycline drug conjugate is provided in a sterile container in liquid, frozen or lyophilized form.

55. (Original) The kit of claim 54, wherein the monoclonal antibody-anthracycline drug conjugate is diluted or reconstituted for patient administration.

56. (Original) The method of claim 43, further comprising administering one or more immunomodulators.

57. (Original) The method of claim 44, further comprising administering one or more immunomodulators.

58. (Original) The method of any one of claims 45 or 46, further comprising administering one or more immunomodulators.

59. (Original) The method of claim 56, wherein said immunomodulators are selected from the group consisting of interferons, cytokines, stem cell growth factors, colony-stimulating factors, lymphotoxins and other hematopoietic factors.

60. (Original) The method of claim 59, wherein said interferon is α -interferon, β -interferon or γ -interferon.

61. (Original) The method of claim 59, wherein said hematopoietic factors are selected from the group consisting of interleukins, colony stimulating factors, granulocyte macrophage-colony stimulating factor.

62. (Original) The method of claim 61, wherein said interleukin is selected from the group consisting of IL-1, IL-2, IL-3, IL-6, IL-10, IL-12, IL-18, and IL-21.

63. (Original) The method of claim 59, wherein said hematopoietic factor is selected from the group consisting of erythropoietin, thrombopoietin, G-CSF and GM-CSF.

64. (Original) The method of claim 59, wherein said immunomodulator or hematopoietic factor is given before, during, or after immunconjugate therapy.

65. (Original) The method of claim 59, wherein said immunomodulator enhances the effectiveness of said conjugate.

66. (Original) The method of claim 57, wherein said immunomodulators are selected from the group consisting of interferons, cytokines, stem cell growth factors, colony-stimulating factors, lymphotoxins and other hematopoietic factors.

67. (Original) The method of claim 66, wherein said interferon is α -interferon, β -interferon or γ -interferon.

68. (Original) The method of claim 66, wherein said hematopoietic factors are selected from the group consisting of interleukins, colony stimulating factors, granulocyte macrophage-colony stimulating factor.

69. (Original) The method of claim 68, wherein said interleukin is selected from the group consisting of IL-1, IL-2, IL-3, IL-6, IL-10, IL-12, IL-18, and IL-21.

70. (Original) The method of claim 66, wherein said hematopoietic factor is selected from the group consisting of erythropoietin, thrombopoietin, G-CSF and GM-CSF.

71. (Original) The method of claim 66, wherein said immunomodulator or hematopoietic factor is given before, during, or after immunconjugate therapy.

72. (Original) The method of claim 66, wherein said immunomodulator enhances the effectiveness of said conjugate.

73. (Original) The method of claim 58, wherein said immunomodulators are selected from the group consisting of interferons, cytokines, stem cell growth factors, colony-stimulating factors, lymphotaxins and other hematopoietic factors.

74. (Original) The method of claim 73, wherein said interferon is α -interferon, β -interferon or γ -interferon.

75. (Original) The method of claim 73, wherein said hematopoietic factors are selected from the group consisting of interleukins, colony stimulating factors, granulocyte macrophage-colony stimulating factor.

76. (Original) The method of claim 75, wherein said interleukin is selected from the group consisting of IL-1, IL-2, IL-3, IL-6, IL-10, IL-12, IL-18, and IL-21.

77. (Original) The method of claim 73, wherein said hematopoietic factor is selected from the group consisting of erythropoietin, thrombopoietin, G-CSF and GM-CSF.

78. (Original) The method of claim 73, wherein said immunomodulator or hematopoietic factor is given before, during, or after immunconjugate therapy.

79. (Original) The method of claim 73, wherein said immunomodulator enhances the effectiveness of said conjugate.

80. (Original) A conjugate of an anthracycline drug and an antibody, wherein said anthracycline drug and said antibody are linked via a linker comprising a hydrazide and a maleimide and wherein an immunomodulator is further conjugated to said antibody.